

EXHIBIT B

COMMONWEALTH OF MASSACHUSETTS

MIDDLESEX, ss.

SUPERIOR COURT DEPARTMENT
OF THE TRIAL COURT
CIVIL ACTION No. 2013-03400-O

IN RE: CONSOLIDATED FRESENIUS CASES

**MEMORANDUM OF DECISION AND ORDER ON FRESENIUS' MOTION
PURSUANT TO DAUBERT v. MERRELL DOW PHARMACEUTICALS, INC., AND
COMMONWEALTH v. LANIGAN TO LIMIT THE OPINIONS AND TESTIMONY OF
DR. CLARK COLTON AND DR. ANDREW ZYDNEY**

Defendants Fresenius Medical Care Holdings, Inc., Fresenius USA, Inc., Fresenius USA Manufacturing, Inc., Fresenius USA Marketing, Inc., and Fresenius USA Sales, Inc. (collectively, “Fresenius”) have moved to exclude the testimony of chemical engineers Dr. Clark Colton (“Dr. Colton”) and Dr. Andrew Zydny (“Dr. Zydny”) on the basis that the mathematical model they created is unreliable. For the following reasons, Fresenius’ motion is **ALLOWED**.

BACKGROUND

Dr. Colton and Dr. Zydny created a mathematical model in order to predict post-dialysis serum bicarbonate levels based upon the amount of acetate that metabolizes in the patient’s blood. See Dr. Colton Opening Report (Exhibit 11 to Fresenius’ Motion), at 8 (explaining that their objective was “to investigate how dialysate prepared with GranuFlo interacted with hemodialysis patients as compared to dialysates containing only bicarbonate. . . . [by] simulat[ing] the intradialytic period during hemodialysis with GranuFlo dialysate . . . and . . . calculat[ing] the variation in plasma concentrations of acetate and bicarbonate with time . . . through the entire interdialytic period”); Dr. Colton Opening Report (Exhibit 11 to Fresenius’

Motion), Appendix 4 (summarizing “Model Equations”), Appendix 5 (setting forth results of simulations using “Model Equations”); Dr. Zydny Opening Report (Exhibit 6 to Fresenius’ Motion), Exhibit C (summarizing “Mathematical Model”). Initially, they applied their model to patient data collected in 1964 and 1984, see Dr. Zydny Opening Report (Exhibit 6 to Fresenius’ Motion), at 80, 81, and the “model clearly show[ed] that: (a) the presence of acetate in GranuFlo increases the initial rise in the serum bicarbonate concentration in the dialysis patient and (b) the final (steady-state) bicarbonate concentration in the serum can be greater than the bicarbonate concentration in GranuFlo and NaturaLyte.” Dr. Zydny Opening Report (Exhibit 6 to Fresenius’ Motion), at 4.¹

Thereafter, Dr. Zydny and Dr. Colton applied their mathematical model to the data from the Acid-Base Composition with Use of hemoDialysates Study (“ABChD Study”) and to the study that Fresenius conducted in Portugal (“VFX Study”). Dr. Colton Supplemental Report (Exhibit 9 to Plaintiffs’ Opposition), at 2; Dr. Zydny Supplemental Report (Exhibit 1 to Plaintiffs’ Opposition), at 1, 3.

“The ABChD Study . . . includes data for both the bicarbonate and acetate concentrations for 11 patients treated using dialysate solutions containing NaturaLyte . . . or GranuFlo. . . . The [VFX] Study . . . includes data for 16 hemodialysis patients treated using a dialysate solution containing 6 mEq/L acetate (along with results for an additional 151 patients treated by

¹ According to Dr. Colton, he and Dr. Zydny “set out to find the answer to the following question: If a patient undergoes hemodialysis with a dialysate having a bicarbonate concentration [in a certain amount] and acetate concentration [in a certain amount], how does the temporal variation of plasma bicarbonate . . . and plasma acetate behave? Does it follow a pattern that would be observed if the dialysate had a [particular] composition . . . ?” Dr. Colton Opening Report (Exhibit 11 to Fresenius’ Motion), at 16. They were able to answer the question in part “without resorting to a mathematical model” and concluded that “if a patient is dialyzed with a dialysate containing 35 mEq/L bicarbonate and 8 mEq/L acetate, the response of the patient is the same as if the dialysate contained 43 mEq/L bicarbonate.” Dr. Colton Opening Report (Exhibit 11 to Fresenius’ Motion), at 17. “The only issue remaining” to apply the mathematical model to “deals with the rate of acetate conversion to bicarbonate. Is it fast enough to be considered instantaneous?” Id. They concluded that after dialysis ends “and throughout the interdialytic period of several days, the patient bicarbonate concentration will be **exactly** the same as would occur with a dialysate bicarbonate concentration of 43 mEq/L.” Dr. Colton Opening Report (Exhibit 11 to Fresenius’ Motion), at 23 (bold in original).

hemodiafiltration and 19 patients treated with a combination of hemodiafiltration and hemodialysis). These two studies provide a unique opportunity to test the ability of the model to describe the acetate and bicarbonate concentrations in the blood during hemodialysis for patients treated with dialysate solutions containing both acetate and bicarbonate.”

Dr. Zydny Supplemental Report (Exhibit 1 to Plaintiffs’ Opposition), at 3. Dr. Colton and Dr. Zydny concluded that their mathematical model

“is in very good agreement with experimental data from both the ABChD and [VFX] Studies, providing validation of the modeling approach . . . [and that their] previous conclusions about the affects [sic] of acetate in the dialysate are both completely correct: the presence of acetate leads to a greater increase in the serum bicarbonate concentration and the final (steady-state) concentration of bicarbonate can (and often does) exceed the bicarbonate concentration in the dialysate – this occurred in 4 out of 16 hemodialysis patients in the Portugal Study and 1 out of 11 patients in the ABChD Study when using GranuFlo.”

Dr. Zydny Supplemental Report (Exhibit 1 to Plaintiffs’ Opposition), at 3-4; see Dr. Colton Supplemental Report (Exhibit 9 to Plaintiffs’ Opposition), at 2-4.

With respect to their analysis of the data from the ABChD Study, Dr. Colton and Dr. Zydny estimated the blood flow rate for each patient in that study because they believed that they did not have that data. See Dr. Colton Supplemental Report (Exhibit 9 to Plaintiffs’ Opposition), at 8; Dr. Zydny Supplemental Report (Exhibit 1 to Plaintiffs’ Opposition), at 16, 17;² Hearing Transcript (10/14/2015), at 223-224; see Dr. Sargent Supplemental Rebuttal Expert Report, pars. 6-7.

The court provided the Plaintiffs with the opportunity for Dr. Colton and Dr. Zydny to supplement their reports with the actual data from the ABChD Study, and provided Fresenius with the opportunity for its expert, chemical and mechanical engineer Dr. John A. Sargent (“Dr. Sargent”) to respond to their supplemental reports. Hearing Transcript (10/14/2015), at 235-236;

² In fact, Fresenius pointed out at day one of the hearing on this motion, this information “actually was available to them. They missed it. They didn’t see that the flow rates were available.” Hearing Transcript (10/14/2015), at 222.

Hearing Transcript (10/15/2015), at 4. Accordingly, on October 21, 2015, Dr. Colton and Dr. Zydney submitted a joint Second Supplemental Expert Report, and Dr. Sargent submitted a Second Supplemental Rebuttal Expert Report on October 28, 2015. The court held a further hearing on this matter on November 19, 2015.

DISCUSSION

When the testimony of an expert is challenged, the court acts as a gatekeeper by conducting “a preliminary assessment of whether the reasoning or methodology underlying the testimony is scientifically valid, and of whether that reasoning or methodology properly can be applied to the facts in issue.” Daubert v. Merrell Dow Pharmas., Inc., 509 U.S. 579, 592-593 (1993); see Commonwealth v. Lanigan, 419 Mass. 15, 26 (1994) (adopting Daubert, in part). The purpose of this preliminary assessment “is to prevent an expert from offering testimony to a fact finder that is not based on reliable methodology.” Canavan’s Case, 432 Mass. 304, 315 (2000). The court’s gatekeeping function “is the same regardless of the nature of the methodology used: to determine whether ‘the process or theory underlying a scientific expert’s opinion lacks reliability [such] that [the] opinion should not reach the trier of fact.’” Id. at 313 (2000) (alterations in original), quoting Lanigan, 419 Mass. at 26; see Daubert, 509 U.S. at 593-594 (setting forth factors for court to consider when determining whether expert’s theory is “scientific knowledge” that will assist jury); Palandjian v. Foster, 446 Mass. 100, 111 (2006) (“Not all of the factors identified in Daubert will be applicable in every case; a trial judge accordingly has broad discretion to determine how to assess the reliability of expert testimony.”).³

³ Even if this court applied the standard as articulated in Milward v. Acuity Specialty Prods. Grp., Inc., 639 F.3d 11 (1st Cir. 2011), the result would be the same. See id. at 16 (“So long as an expert’s scientific testimony rests upon “good grounds”, based on what is known,’ . . . it should be tested by the adversarial process, rather than excluded for fear that jurors will not be able to handle the scientific complexities” (quoting Daubert, 509 U.S. at 590)).

Fresenius asks this court to preclude Dr. Colton and Dr. Zydney from testifying at trial about the mathematical model that they developed. For the following reasons, the mathematical model is unreliable, not only in a general sense, but also in the way in which Dr. Colton and Dr. Zydney have applied the model to actual patient data from the ABChD and VFX Studies.^{4, 5}

I. The Mathematical Model Itself

The mathematical model that Dr. Colton and Dr. Zydney developed is unreliable for a number of reasons. First, they premise many of their opinions on the condition of “steady state” whereby the patient’s “concentrations remain stable (constant) as a function of time; further dialysis would cause no change in the serum concentrations.” Dr. Zydney Opening Report (Exhibit 6 to Fresenius’ Motion), at 12; see Fresenius’ Motion, at 3 n.3 (citing to opinions in Dr. Colton’s and Dr. Zydney’s reports that are premised on this condition). As Fresenius points out, and as Dr. Colton and Dr. Zydney acknowledge, the condition of “steady state” never occurs in a dialysis patient. See Fresenius’ Motion, at 3. There is, consequently, no meaningful data as to this condition. The use of this condition in the model therefore contributes to its unreliability.

Second, Dr. Colton and Dr. Zydney assume that the volume of distribution of acetate in the body is the same as the volume of distribution of bicarbonate. See Dr. Sargent Second Supplemental Rebuttal Expert Report, par. 4. This assumption causes their model to overestimate the total concentration of bicarbonate in the body. See *id.* The Plaintiffs’ own expert, Dr. David Goldfarb testified to the contrary at his deposition, agreeing with the statement “that the volume of distribution of bicarbonate is not the same as the volume of distribution of

⁴ The court notes that the ABChD Study and the VFX Study are of limited value themselves given the small data set of each study. See Dr. Zydney Supplemental Report (Exhibit 1 to Plaintiffs’ Opposition), at 3.

⁵ At day two of the hearing on this motion, counsel for the Plaintiffs represented that Dr. Colton and Dr. Zydney have opinions that do not depend on their mathematical model. This decision does not address any such opinions, nor does Fresenius challenge those opinions under Daubert-Lanigan.

acetate[.]” Dr. Goldfarb Deposition (Page 8 of Fresenius’ 11/19/2015 PowerPoint Presentation), at 257.

Third, this mathematical model has not been published or otherwise peer reviewed. While not dispositive as to admissibility, Daubert, 509 U.S. at 594, this deficiency combined with those discussed above, as well as the fact that the model is litigation driven and has “evolved” in order to conform with the ABChD and VFX Studies, as discussed below, contributes to a finding that the mathematical model is unreliable. In fact, Dr. Colton himself testified at his deposition that, “before [he] would ever advise a nephrologist to rely on [the model] for prescription, [he] would want to see data that can be compared with prediction and to assess how good the model is in the framework of how the patients are treated today, and the extent to which there are aberrations” Dr. Colton Deposition (Exhibit 5 to Fresenius’ Motion), at 122.

II. Application of the Mathematical Model to Patient Data

The mathematical model is also unreliable to the extent Dr. Colton and Dr. Zydny attempt to apply it to the data from the ABChD and VFX Studies. First, most recently, when applying the model to the actual patient blood flows from the ABChD Study, Dr. Colton and Dr. Zydny modified the model by “includ[ing] the effects of ultrafiltration using the reported ultrafiltration volume” Dr. Colton and Dr. Zydny Second Supplemental Expert Report, at 8. Dr. Sargent explained that, the incorporation of ultrafiltration only for the data from the ABChD Study “is not [merely] an adjustment of parameters This is a fundamental change to the model . . . that they only apply to certain data and not others. If a model requires a fundamental change in order to fit a large portion of the data sets against which it is tested, it is not a reliable model.” Dr. Sargent Second Supplemental Rebuttal Expert Report, par. 4.

Second, Dr. Colton and Dr. Zydny's assessment of agreement between its model and the ABChD Study revealed that “[a]greement was good for four patients, but the serum bicarbonate concentration . . . at the end of dialysis (4 hrs.) was substantially below predictions of the model for three patients. Agreement was fair for the other four patients.” Dr. Colton and Dr. Zydny Second Supplemental Expert Report, at 3; see Dr. Colton and Dr. Zydny Second Supplemental Expert Report, at 35 (Table B-2). Therefore, even with the incorporation of ultrafiltration, there was still “low” agreement, see Dr. Sargent Second Supplemental Rebuttal Expert Report, par. 5; and even as to the “good” agreement, there was still an “under estimation of early bicarbonate numbers and a crossover mid treatment.” Dr. Sargent Second Supplemental Rebuttal Expert Report, par. 9, citing Dr. Colton and Dr. Zydny Second Supplemental Expert Report, at 11 (Figure 3).

Third, with respect to the VFX Study, “Dr. Colton [but not Dr. Zydny] tried to draw a connection between the hemodiafiltration patients and hemodialysis patients and say . . . [they are] ‘indistinguishable[.]’” Hearing Transcript (10/14/2015), at 225; see id. (explaining difference between hemodiafiltration and hemodialysis); see also Dr. Colton Supplemental Report (Exhibit 9 to Plaintiffs' Opposition), at 2 (opining that “data from both [hemodialysis] and [hemodiafiltration] patients in the VFX study represent populations that are indistinguishable, i.e., they behave similarly”). “While it may be true that the patients are indistinguishable, the treatments are not and this characterization does not apply to the data from these very different treatment methods.” Dr. Sargent Supplemental Rebuttal Expert Report, pars. 11-12 (underlining omitted). Moreover, Dr. Colton’s method of analyzing this data “does not support his conclusions.” Dr. Sargent Supplemental Rebuttal Expert Report, pars. 14-15.

Finally, when Dr. Zydny applied the mathematical model to the VFX Study, he opined that that “[f]our of the 16 patients had a final bicarbonate concentration that was equal or greater than that in the dialysate solution . . . thus provid[ing] conclusive evidence in support of . . . [their] conclusion that the final bicarbonate concentration can be greater than the bicarbonate concentration in the dialysate solution when using a dialysate that contains acetate in addition to bicarbonate.” Dr. Zydny Supplemental Report (Exhibit 1 to Plaintiffs’ Opposition), at 11 (bold omitted). As counsel for Fresenius argued at day one of the hearing on this motion, however, assuming that Dr. Colton and Dr. Zydny’s “model was okay at lining up with the [VFX] Study,” there are demonstrable deficiencies, noted above, when applying it to the ABChD Study; the court cannot permit “a model that is right half the time and wrong half the time get put in front of jury . . . We have to throw the model out.” Hearing Transcript (10/14/2015), at 227; see Daubert, 509 U.S. at 594 (listing “rate of error” among factors for court to consider).

III. Conclusion

The mathematical model that Dr. Colton and Dr. Zydny created is unreliable, and they are precluded from testifying about this model at trial. Accordingly, Fresenius’ motion is **ALLOWED**.

ORDER

For the foregoing reasons, the court **ORDERS** that Fresenius’ Motion to Limit the Opinions and Testimony of Dr. Clark Colton and Dr. Andrew Zydny is **ALLOWED**.

SO ORDERED this 24th day of November, 2015.



Maynard M. Kirpalani
Justice of the Superior Court